WELLCOME INSTITUTE LIBRARY
Coll. welTROmec
Call No. Dam WC75 1907 R72a

THE MILROY LECTURES

on

KALA-AZAR, ITS DIFFERENTIATION AND ITS EPIDEMIOLOGY

L. Rogers

Lecture III - The life history of the Parasite, mode of infection and prophylaxis.

Lancet, 1907, i.

22200122325

WELLCOME INSTITUTE
LIBRARY
Coll. WellTPOmnec
Call
No.

THE LANCET.

A Journal of British and Foreign Medicine, Surgery, Obstetrics, Physiology, Chemistry, Pharmacology, Public Health, and News.

IN TWO VOLUMES ANNUALLY.

VOL. I. FOR 1907.

EIGHTY-FIFTH YEAR.

LONDON:

PRINTED AND PUBLISHED BY THE REGISTERED PROPRIETORS, AT THE OFFICES OF "THE LANCET," No. 423, STRAND, AND Nos. 1 & 2, BEDFORD STREET, STRAND.

MCMVII.

constitutional symptoms being relieved, the necessity for general extraction is eliminated and the use of artificial substitutes obviated. In a mouth affected by alveolar pyorrhœa nothing is of greater disadvantage to existing and healthy teeth than tooth plates, fit they never so well.

In surveying the facts and arguments set out the relationship of alveolar pyorrhœa (or alveolar osteitis, being more in accord with the pathology of the affection) to many complex symptoms manifested in parts of the body more or less remote from the jaws is explainable by infection from the gums as proved by the bacteriological evidence, such evidence pointing to the infection of the rest of the body, sometimes by the organisms themselves, at other times by their products. Some direct evidence and much circumstantial evidence adduced point to the infection taking place through the gum tissue as well as the direct ingestion of bacteria or their products. The infection has been traced to its causative agents by means of the opsonic index of the individual's blood to organisms obtained from the local disease, which points clearly to the origin of the lowering of the general resistance of the individual and the increased susceptibility of the whole of the body favouring secondary invasions. In seeking the etiology and origin of the affection evidence has been adduced strongly suggesting the derivation of the infecting bacteria from a common source of infection—milk. The knowledge obtained of the lowering of general resistance to certain organisms gives a method of treatment somewhat laborious no doubt, but giving a logical and practical method of dealing with the disease.

ABSTRACT OF

The Milroy Lectures

ON

KALA-AZAR, ITS DIFFERENTIATION AND ITS EPIDEMIOLOGY.

Delivered before the Royal College of Physicians of London

BY LEONARD ROGERS, M.D. LOND., F.R.C.P. LOND.,

MAJOR, I.M.S.; PROFESSOR OF PATHOLOGY AT THE MEDICAL COLLEGE, CALCUTTA.

LECTURE III.[1]

Delivered on Feb. 28th.

THE LIFE HISTORY OF THE PARASITE, MODE OF INFECTION, AND PROPHYLAXIS.

MR. PRESIDENT AND GENTLEMEN,—I have now dealt with kala-azar both collectively as an epidemic and individually as a disease but have still briefly to discuss the evidence I obtained in Assam regarding its infectiousness before describing the life history of the parasite which produces it.

When I went to Assam in 1896 there was much difference of opinion as to whether kala-azar was infectious or not, the majority holding that since it was undoubtedly malarial it therefore could not be infectious, while a few contended that it was certainly a communicable disease and therefore it could not be simply malarial in nature, but no one had found time to inquire closely into the exact way in which it spread. In order to settle this important point I travelled over 150 miles on foot from village to village obtaining the histories of the introduction of the disease into them from the head men, who return all the deaths, and who were always able to give me detailed information on the subject. Very similar stories were constantly related to the effect that someone suffering from the disease had come to live in the village, usually with relatives, and shortly afterwards others residing in the same house were attacked, and on the survivors of the first infected household being taken into other families they in turn suffered, while after a year or two the disease became widespread and frequently from one-third to two-thirds of the people died from it before it began markedly to decrease. Wherever the infection had spread a similar kind of history was obtained, while whenever a village escaped, although surrounded by infected ones, it was found that for some reason or other they had no communication with each other, even if only a few hundred yards apart. Thus a small village of Brahmins, who had no intercourse with the low caste people around them, escaped, although all the surrounding villages had been attacked for several years past. Again, one part of a village which was separated from the rest by only a few small ricefields remained free for years owing to the head man not allowing them to have any intercourse even with their own relations in the infected portion. On the other hand, on visiting a village which was reported to be attacked, although all those around it were free, I found that it belonged to people who had recently moved there from a badly infected part of the district bringing the disease with them.

The extreme steps which the people sometimes took to prevent the spread of the disease afford also strong evidence of its infectiousness in their eyes. For example, a girl who had married a man in a healthy village, but who soon after was found to be suffering from kala-azar, was turned out, while even her own father in another neighbouring uninfected village was prevented from taking her into his house, so she was living in a grass hut erected in the open rice fields at the time of my visit. A similar plan of isolating cases was adopted by the Garos, who are reported to have gone so far as to render the kala-azar patients comatose with drink and then to burn them in their huts. All the evidence goes to show that the infection is, as a rule, obtained by sleeping in a house containing infected persons for a longer or shorter time, in some cases only for a day or two. Moreover, the plan of moving the village to a new site appeared to have a distinctly good effect in lessening the disease when occasionally resorted to by the people themselves, so that I thought the infection might possibly pass through the soil. It was on the knowledge of the infection being largely a house one that I based the prophylactic measures which proved so successful long before the parasite of kala-azar was discovered, but now that we possess much more definite information regarding the true pathology of the disease it will be best to describe the life history of the protozoal organism of kala-azar before taking up the important practical question of prophylaxis, as the latter will thus be rendered more definite.

THE PARASITE OF KALA-AZAR AND ITS DISTRIBUTION IN THE HUMAN BODY.

The parasite of kala-azar was independently found by more than one observer, but to W. B. Leishman belongs the credit of having had the courage first to describe it two and a half years after he had detected it, as probably a degenerate stage of a human trypanosoma, not very long after that organism had been found in a fever in Africa by the late Dr. J. E. Dutton, while Rose Bradford and Plimmer had previously described a form of the trypanosoma Brucei similar to the bodies which Leishman found. As soon as Leishman's paper reached India C. Donovan recorded that he had independently observed the same bodies in the spleens of patients dying from prolonged fevers in Madras one month before Leishman's note was published, and as he was able to find them in fresh spleen blood obtained by puncturing that organ during life he was able to disprove Leishman's suggestion that they were degenerate trypanosomes, for the flagellate form of the organism has never been found in the human system. Laveran and Mesnil, after examining specimens sent by Donovan, concluded that the organism was a piroplasma, while Dr. J. H. Wright of Boston at the end of 1903 described similar bodies to those of Leishman and Donovan in a form of chronic ulceration met with in the Punjab known as Delhi boil, in which D. D. Cunningham as early as 1885 had described the aggregations of these peculiar bodies. As kala-azar is unknown in the Punjab there is every reason to believe that the parasite of Delhi boil is quite a distinct species from that of the Assam fever.

In 1896 I had stained smears of kala-azar spleens with aniline dyes without being able to distinguish these bodies, which are not well brought out by them, while Romanowsky's stain and its numerous modifications had not then come into general use, and I mainly used fresh unstained films, as then advised by Sir Patrick Manson, for searching for malarial and other protozoal parasites. The papers just referred to appeared while I was on leave in England, and I quickly realised, as was also suggested by Donovan, Ross, and others, that if many of the cases previously known as "malarial cachexia" were in reality caused by the new parasite, then kala-azar of Assam must also be produced by it, for I had

[1] Lectures I. and II. were published in THE LANCET of Feb. 23rd (p. 486) and March 2nd (p. 568), 1907, respectively.

shown in my report that the Assam outbreak was but an epidemic form of the so-called "malarial cachexia." On returning to India at the end of 1903 I obtained some slides of spleen blood of kala-azar patients from my friend Mr. J. Dodds Price, and readily found the new parasite in them, as well as in several cases of the chronic spleen fever of Dinajpur which were evidently the sporadic form of the same disease. At about the same time Dr. C. A. Bentley independently found the same parasite in kala-azar and published his observations shortly before my own appeared in print. Other cases in Dinajpur with large spleens following chronic fever showed only malarial parasites in their spleen blood, and I found it impossible at a single clinical examination to differentiate between the two forms of the disease, although subsequently able to do so by the blood changes described in my last lecture. It is not therefore surprising that kala-azar has been so long confounded with chronic forms of malarial fever, and the discovery of the new parasite has done more towards clearing up the fevers of Bengal and some other parts of India than anything since Laveran's description of the parasites of malaria. Over a year later S. P. James also recorded having found the Leishman-Donovan bodies in 67 out of 68 cases of kala-azar, and gave some valuable clinical information regarding the differentiation of this disease from chronic malaria, the discovery of the new parasite having furnished the key to the problem which a century of clinical observations had been unable to unlock.

Distribution of the parasite in the human body.—It soon became apparent from the observations of Manson and Low, Ross, and especially of Christophers (who had been placed on special duty by the Government of India to work at the subject in Madras), that the organisms may be found in practically every organ of the body in variable numbers, although most numerous in the spleen, the bone marrow and the liver. They were also observed occasionally in the mesenteric glands and rarely in ulcers in the intestines, and both Manson and Christophers suggested that they might escape in the fæces and so reach water through which reinfection might take place. When a little later I discovered the flagellate form of the parasite, Bentley announced that he found trypanosomes more commonly in fish from near kala-azar infected lines than elsewhere, and suggested that they were a stage of the human parasite, so I made some observations in the same year to test this hypothesis in Nowgong, but was unable to confirm his statements as far as that district was concerned.

Now Christophers's microscopical studies showed that the parasites multiplied mainly in the large endothelial or macrophagic cells of the spleen and bone marrow until the invaded cells bulge into the lumen of the vessels. During the operation of spleen puncture those containing the largest parasites rupture most readily and the organisms thus obtained are nearly all the larger capsulated ones in contrast with the minute ones which are most numerous in a spleen smear made post mortem. A similar rupture of the distended endothelial cells must also frequently take place naturally in the body and so allow of the entrance of the parasite into the circulating blood and its distribution to all parts of the body, a hypothesis which also explains the large number of the organisms found in just those organs where the malarial parasites also accumulate—namely, the spleen, the bone marrow, and the liver; while I have also several times found them in the brain.

This leads me to the consideration of the frequency of the parasite in the peripheral blood, for it was the supposed great rarity of such incidence which gave rise to the theory of its escape from the large bowel as the source of infection which was so generally held before my discovery of the flagellated stage of the parasite. Yet Donovan, Christophers, and James have all met with the parasites within the leucocytes, chiefly in the polynuclears, although no one has confirmed the statements of Donovan, Laveran, and Mesnil that they may be seen within the red corpuscles, other workers considering that they are only rarely seen living on the surfaces of the red discs. Recently Donovan has reported that he has found the parasites in the peripheral blood of 75 per cent. of his patients, while W. S Patton, now on special duty in Madras, informs me that he detected them in a still larger proportion of specially selected advanced cases. Donovan stated that they are most easily found during high fever, but I have been unable to confirm this, while it is also contrary to Patton's experience, who finds that they are commonest in the later stages of the disease, so that it is doubtful if a microscopical examination of the finger blood for the parasites will prove of much diagnostic value in the difficult early stages of the disease. In a few cases I have tried the plan of quickly centrifuging for one minute two or three cubic centimetres of vein blood to separate the majority of the red corpuscles and then making slides of the blood plates and leucocytes after a second longer centrifugation without much success, but I think it is worthy of further trial as it may prove preferable to the sometimes dangerous spleen puncture as a diagnostic method. However this may be, it is now quite clear that the parasites are at least present in the circulating blood in large numbers in most advanced cases, quite sufficiently so readily to allow of their entering the stomach of any blood-sucking insect which might form a suitable host for its further development.

THE CULTIVATION AND DEVELOPMENT OF THE FLAGELLATED STAGE OF THE PARASITE.

Up to July, 1904, the only stage of the parasite known was the small oval body of about the size of a blood plate, with a rounded macronucleus and a smaller rod-shaped micronucleus or centrosome, such as are shown in the first line of the plate. These multiplied by division so that in spleen smears a number of very small bodies may be seen in a single cell with no very definite capsule, but recognisable by the double nucleus, or numbers of them might be found in a hazy material, first taken for a zooglea mass, but now known to be but the protoplasm of the cell in which they were growing. It is not surprising, then, that there was much speculation as to the precise class of protozoa to which this organism belonged, suggestions varying from degenerated trypanosoma of Leishman, piroplasma of Donovan and Laveran, spores of a mirosporidian of Christophers, and an entirely new genus which Ross proposed to call Leishmania-Donovani in honour of the two observers who first described the parasite, being put forward.

As it was clear that we could not expect to gain much further knowledge of the exact nature of the parasite until we learnt something of the extra-corporeal stages and the discovery of such further portions of its life history was alone likely to throw valuable light on the mode of infection of the disease it produces, I set to work on these lines as soon as possible after my return to India and was fortunate enough to obtain important results. The method employed was to obtain blood containing the organism by means of spleen puncture and to add to it about one cubic centimetre of sterile salt solution, containing a little citrate of soda to prevent the blood clotting, and to examine it frequently to see what became of the parasites. My first attempts were made at blood heat, with the result that they all died out in a day or two, as other workers had also found. Being struck with the resemblance of the macro- and micronucleus of the parasite to those of trypanosomes, just as Leishman had been, and remembering that Laveran and Mesnil had succeeded in keeping the latter organism alive for a much longer time at a low temperature than at blood heat, I next tried incubating the citrated blood at about 27° C. and found that in this way they lived, or at least retained their staining properties, for several days, and, what is more, they appeared to multiply considerably, many dividing forms being present, but as yet without any other material alteration. On next reducing the temperature to about 22° C. (an ice incubator having to be used during most of the year in Calcutta for this purpose) I was soon rewarded by finding that not only did the parasites unquestionably multiply rapidly, but they also increased in size and developed a blue-staining protoplasm, and after a time the further development of flagellated forms took place, which were actively motile.

The different stages of this remarkable development are shown in the diagram, which has been made from a plate published in a paper in the Proceedings of the Royal Society last year, all the forms in which have been accurately drawn to the same scale with a camera lucida, thus illustrating the extraordinary increase in the size of the parasite as well as in its numbers. Whereas the human stage of the parasite appears to be no larger than a blood plate and requires careful search with an oil immersion lens for its detection, yet the large rosettes shown in the lower part of the diagram can readily be seen as a stained mass or in unstained specimens as a lighter circular area among the red corpuscles with a half-inch lens. The form in which the parasite is found in the human body is shown in the first line of the plate. The

DESCRIPTION OF PLATE.

Magnification of all the figures 1500 diameters. (From the Proceedings of the Royal Society, B. Vol. LXXVII., Plate 7.)

Fig. I., Undeveloped Leishman-Donovan bodies from spleen puncture film. Fig. II., Early stages of development, from two days' culture in acidified citrated blood; 1 and 2, body and macronucleus enlarged; 3 and 4, first appearance of eosin body; 5 and 6, elongation and subdivision; 7 and 8 first appearance of flagellum. Fig. III., Stages of division of the early flagellated forms. Fig. IV., Double long swimming forms. Fig V., Fully developed long, free, active single cells. Fig. VI., Degenerate forms. Fig. VII., Undeveloped forms in a white corpuscle. Fig. VIII., Early stages of development in a degenerating white corpuscle. Fig. IX., Stage in the formation of rosette. Fig. X., Separated flagella with micronuclei attached. Fig. XI., Rosette breaking up into free forms. Fig. XII., Small complete rosette.

earliest stages of this development, which are shown in the second line of the plate, consist in an enlargement of the macronucleus without any corresponding change in the micronucleus, which remains a small rod throughout the whole process. At the same time the protoplasm, which is clear in the spleen form of the parasite, now becomes much increased in quantity and takes on a blue colouration with Romanowsky's stain, Leishman's modification of which was used throughout this inquiry. The next change is a curious one—namely, the appearance in the protoplasm of a rounded mass which takes on the red element of the stain, so may well be termed the eosin body, and the micronucleus is always found to be closely attached to it, while the flagellum always arises from it. This form is seen in Nos. 3 to 5 of line II., while the last two forms of that line show the flagellum arising from it and apparently separated from the micronucleus by a narrow unstained space, although a study of degenerating flagellate forms proves that the flagellum is really organically connected with the micronucleus, for it comes away from the body with it, as shown in form X. This flagellated stage rarely appears before the third day in successful cultures, and when the development is carried on under the most favourable conditions (to be described presently) they are found in enormous numbers and showing all the stages of subdivision, which are illustrated in the third line of the diagram.

In this process of multiplication of the flagellated forms the first change is the division of the micronucleus and flagellum into two, next the macronucleus also divides, and then a line appears down the centre of the body splitting it into two, the process being quickly commenced again by both the new forms. In this manner the rapidly dividing forms push each other round, as shown in Fig. IX., until they form a complete rosette of No. XII., the flagella all pointing in towards the centre, and in this stage such groups can readily be seen in fresh specimens by low powers with the flagella actively waving in the middle of the mass. Lastly, the individual forms, which up to now are mostly only two or three times as long as they are broad, gradually elongate out and begin to break away, as shown in No. XI., to form single exceedingly active organisms, which when stained have the appearance shown in line V, the eosin-staining micronucleus and flagellum being both situated at the anterior end of the organism, while the macronucleus still remains about the centre. The forms in line VI. are the retrogressive stages of degeneration resulting from contamination of the culture with staphylococci. Forms VII. and VIII. show early development within a polynuclear leucocyte.

For a long time I was in doubt whether this flagellated form was but a stage in the development of a trypanosome, similar to those of the culture forms of that of bird trypanosomes obtained by Novy and McNeal on blood agar medium—a method of culture which I have failed to obtain success with in any stage of the kala-azar parasites. Now that extremely numerous, very active, and apparently fully developed flagellate forms have been obtained, without any tendency for the micronucleus even to approach the macronucleus being seen, much less any sign of an undulating membrane, I have come to the conclusion that the parasite is not a partially developed trypanosome but another kind of flagellated organism.

THE NATURE OF THE PARASITE.

The discovery of the flagellated stage of the parasite affords much help in classifying it, for now that the life history of the piroplasma canis has been worked out and it is known that it has no flagellated stage, the suggestion of Laveran and Mesnil that the kala-azar parasite belongs to that genus may be put out of court. It also appears from what has just been said that it is not a trypanosome, and it appeared to me to be more closely allied to the herpetomonas than to any other known flagellate protozoon. As repeatedly sending specimens to English zoologists failed to elicit any opinion on the point I forwarded some to the late Professor Schaudinn, unfortunately too late to obtain an answer before his lamented death, but I received an early reply from Dr. Hartmann of the Hamburg School of Tropical Medicine, which was to the effect that the organism differs from all hitherto known flagellates; so it may most conveniently be named the Leishmania-Donovani, as suggested by Ross, while he also informed me this was the opinion of Professor Schaudinn, so it may safely be adopted.

Such a startling discovery as that just related necessarily needed confirmation before being generally accepted, but this was soon supplied by Assistant-Surgeon G. C. Chatterjee working in my own laboratory, and some three months later independently by Christophers in Madras (the publication of whose observations was much delayed by the Government regulations applying to him), while several months later still J. Statham, R.A.M.C., and Leishman also confirmed my work in England.

CONDITIONS AFFECTING THE DEVELOPMENT OF THE FLAGELLATE STAGE.

In my earlier cultures the amount of development obtained was extremely variable, for although in nearly all of them the earlier stages were seen, yet only in a 1 in 6 was the flagellate stage reached, and then usually it was very scantily present as compared with the enormous numbers of slightly developed bodies. This variability and incompleteness of the development pointed to the experimental conditions under which they had been obtained being still far from those most favourable to the extra corporeal stage of the parasite, and led me to carry out a long series of observations extending over a year in order to try to ascertain the optimum conditions for the development, which might be expected to furnish a clue to those under which the flagellate forms exist in nature and so to the probable mode of infection of the disease it causes. Over 100 cultures were made before success was obtained, in the course of which a number of negative conclusions were arrived at which are not without some practical bearing on the problem.

Temperature limitations.—It was early found that a temperature far below that of the human body is essential to success, from 20° to 22° C. being the optimum one, while I have never got very marked development above 25° C., or 77° F., exposures to higher temperatures than this for but a few minutes causing rapid death and degeneration of all the developing forms; a point of the greatest importance in connexion with the season of the year when the infection of the disease takes place, as mentioned in my last lecture. The minimum temperature below which the development will not take place has not yet been absolutely settled, owing to the short cold season in Calcutta, but so far as my observations go they point to from 15° to 17° C. (or about 60° F.) as the lower favourable point, which is in accordance with the seasonal and climatic distribution already given.

Sterility.—Another point of crucial importance is the sterility of the culture tubes, especially as regards micrococci, contamination with bacteria during the frequent examinations of the tubes having been always followed by rapid death and degeneration of these protozoal parasites. Staphylococci exerted the greatest effect in this direction, which affords a possible explanation of the occasional favourable effect on the fever of kala-azar following septic complications already referred to in my last lecture. This necessity for sterility explains why the parasites have never been found in the fæces in those occasional cases in which they are present in the bases of ulcers in the intestine, while it renders this mode of escape from the body as the ordinary source of infection extremely improbable. As I was also unable to obtain any development whatever in even sterile water, this agency, which is probably never sterile in nature when at a temperature suitable to the development of the parasite, may also be put out of court as the common vehicle of infection, especially as all clinical experience is also against it. Different strengths of salt solution were tried and only showed that somewhere about that of the blood or slightly higher degrees were most favourable to the process.

Anaerobic conditions.—An atmosphere of hydrogen or nitrogen gas prevented the development without killing the organism, which might develop well on the cultures being again placed under ordinary atmospherical conditions, once more indicating that the intestinal canal is unfavourable for the process. On the other hand, an atmosphere of oxygen gas in excess did not appear to affect the development.

Acid medium.—All the negative results just mentioned, taken together with a number of facts regarding the conditions influencing the spread of the disease ascertained during its study in Assam, led me to the conclusion that the mode of the infection must be through some biting insect. As the mosquito seemed to be an unlikely agency on account of the strictness with which the infection appeared to be limited to houses containing cases of the disease, I strongly suspected that pest of Indian life, the homely bed bug, to

be the culprit. During some earlier unpublished examinations of the contents of the stomachs of bugs from the beds of plague patients for bacteria I had been struck by the frequency with which the contents were absolutely sterile, a somewhat unexpected result. I therefore tested the reaction of the fluid in the stomachs of these insects after sucking human blood and found it to be distinctly acid, the secretions of the organ being evidently sufficient to neutralise the natural alkalinity of the imbibed blood. This fact led me to try the addition of a drop or two of weak sterile citric acid solution to the infected citrated human spleen blood, and at last my patience was rewarded by obtaining a far more abundant and uniformly complete development of active flagellated forms than I had ever seen before in scores of cultures, the rosette-like groups being especially abundant and active. What was most striking and important was the fact that, instead of the vast majority of the organisms showing little or no development while but very few reached the flagellate stage in the previous alkaline blood cultures, in the acidified medium all the organisms appeared to develop uniformly, so that when about the third day the flagella began to be seen it was found that the vast majority of the organisms, which were multiplying with extreme rapidity, had already reached this advanced degree, and a day or two later few or none remained in the original small undeveloped stage. It was clear, then, that this acidified sterile fluid blood medium kept at a temperature of about from 20° to 22° C. was extremely favourable to the growth of the extra-corporeal stage of the organism and might with a very great degree of probability be relied on to furnish the long-wanted key to the most likely intermediate host of the parasite. All the developmental forms in the diagram have been drawn from one of these acid cultures.

FEEDING EXPERIMENTS.

The success of the acidified blood as a culture medium having now greatly strengthened my suspicion that the bed bug is the carrier of the infection of kala-azar, I next tried a variety of methods to induce these insects to swallow infected human blood placed in sterile capsules of different kinds, but without success, as they refused to be tempted to suck the blood. In order to ascertain if the stomach of these particular insects was likely to prove suitable for the development the plan was next adopted of mixing human spleen blood containing the organisms with about an equal quantity of the fluid contained in the stomachs of these insects after feeding on human blood in sterile capillary tubes, and I succeeded in obtaining the development of fully flagellated forms at the suitable temperature, so that it only remained to find similar forms in these insects after feeding on kala-azar subjects to complete the proof that they may actually carry the infection as far as is possible to do so as long as no animal is known which takes it, for it would not be justifiable to try to infect human subjects with such a deadly disease, and hitherto all attempts to inoculate the ordinary laboratory animals or even monkeys have failed. As far as I know the anthropoid apes have not been experimented upon owing to the difficulty and expense of obtaining them, one orang-outang which I got for the purpose having died too soon to enable this point to be settled.

As sufficiently numerous feeding experiments with such insects to be of any value require much time I spent all the leave I could obtain when the temperature conditions were favourable in Assam last year for this purpose, but although I examined blood from the stomachs of over 200 bugs fed on kala-azar patients with low powers in a fresh condition to look for active flagellate forms I had met with no success when I had to stop on account of my eyes, and have only been able to find time since to examine a few of the stained slides then made. This failure was disappointing, but the time available for the work was so short that I did not regard the negative result as in any way invalidating my theory, and was therefore much pleased to learn several months later that Captain Patton had been placed on special duty to work on similar lines, and still more when it was announced in the *Indian Medical Gazette* that he had obtained some development of the kala-azar parasites in the stomachs of bed bugs, but not in those of mosquitoes, ticks (with which Christophers had previously obtained negative results), or lice. While on a visit to Madras during the last Christmas holidays Captain Patton kindly showed me his specimens, which clearly contained the early stages of the development with the appearance of the eosin body and in one of his drawings a short flagellum was also apparent. They struck me as being very similar to the scanty development I obtained before using acidified media and gave me the impression that the conditions were not those most favourable to the process and on inquiry I found that attention had not been paid to obtaining the most favourable temperature for the development, so I urged him to do as many feeding experiments as possible during the then more favourable cold season, when the optimum temperature could be obtained. The result has fully substantiated my opinion, for within three weeks Captain Patton wrote to me, "I have got the complete cycle of the parasite up to completely developed flagellates," and added, "There is no shadow of doubt that the bed bug transmits the disease."

Much doubtless remains to be done in this direction in order to ascertain exactly in what form the parasite is again inoculated into the human subject. But the long time during which the infection clings to houses points to the possibility of its being transmitted through the progeny of the first affected bugs, just as occurs in the case of the piroplasma of cattle and dogs, so that the ovaries and salivary glands should be carefully examined in fed insects for further stages of the parasite. Nevertheless, our knowledge of the life history of the kala-azar organisms is now sufficiently known to enable the facts to be made practical use of in the prophylaxis of the disease, which is the last portion of my subject remaining to be considered.

THE PROPHYLAXIS OF KALA-AZAR.

I have already mentioned the partial success of moving infected villages to new sites but a short distance away, which, taken with the strong evidence I collected in 1897 as to the infection being a house one, appeared to me to afford the most promising basis for preventive measures. Finding also that over a year before I went to Assam Mr. Dodds Price, suspecting the disease to be infectious, had placed 150 out of 200 freshly imported coolies in newly built lines of houses, while the remaining 50 had to be accommodated in infected lines for want of room, I got him to work out the results of this measure. It was thus ascertained that although none of the 150 in the new lines had suffered from kala-azar during two years they had been on this badly infected tea garden, yet no less than eight, or 16 per cent., of those placed in the old lines were already dead of the disease, and that, too, in spite of the fact that the new lines went but 300 yards from the old ones, a distance insufficient to prevent the spread of malaria through the agency of mosquitoes.

This very important result obtained by Mr. Price encouraged me to suggest the further step of moving all the healthy people out of infected lines to houses on a new site, no person, however, being taken from an infected hut in consequence of the impossibility, at that time, of differentiating the early stages of kala-azar from ordinary malarial fever. This plan was carried out by Mr. Price in the case of a coolie line which was so badly infected that no less than 144 out of 240 souls were either actually suffering from kala-azar or had cases in their households, leaving only 96 who could be moved to the new site, five of whom were very shortly afterwards sent back on account of their developing fever. A large number of fresh coolies were also drafted into these new lines, so that 18 months later it contained 416 souls, among whom not a single case of kala-azar had occurred—a statement which happily remains true at the present time, ten years after they were occupied. In marked contrast with this result is the fact that of 60 coolies who refused to move out of the infected lines no less than 20, or one-third, were attacked within the 18 months, and a year ago they had nearly all been carried off by the disease, although their houses were only 400 yards from the new ones which remained healthy. This experiment was so conclusive that it has since been often repeated with uniformly good results, so that the disease is no longer as dreaded as it used to be by tea-planters in the Nowgong district. In slightly infected lines only the affected households were segregated and their houses were burnt, this measure being also of value, although less effective than the former one. It is only in the few remaining old lines that the infection lingers at the present time, and I am glad of this opportunity of saying that Mr. Price deserves the greatest possible credit for initiating and successfully carrying out these measures, especially as he has been too modest to claim it himself. It is not too much to say that it is now certain that this awful scourge can be robbed of most of its terrors whenever it is possible fully to carry out segregation measures, as on tea

estates, while their success has encouraged the application of the same principles in dealing with the spread in villages as far as they are practicable in that case.

MEASURES TO CHECK THE SPREAD OF KALA-AZAR IN THE VILLAGES.

It was not possible to carry out such complete measures as the above in the infected villages, but the following recommendations of mine proved successful in preventing the spread of the disease into the eastern half of the Brahmaputra valley as already described. In the first place, a pamphlet in the vernacular was widely distributed explaining in simple language the manner in which the infection was spread and the precautions necessary to prevent its introduction into unaffected places, and by thus putting the people on their guard against the insidious invasion of the disease they were often enabled to keep it at bay without having to learn the lesson by bitter experience. In the second place, assistance was given by the Government to already infected villages to remove to a new site, the infected persons being as far as possible accommodated in a separate place.

It may, then, be fairly claimed that much practical good resulted from my inquiries of 1896–97, both in the prevention of the further spread of the disease up the Assam valley and also in its being practically stamped out of the Nowgong tea gardens, and it is worthy of note that all this was accomplished before the exact nature of the disease was ascertained by the discovery of the parasite in 1903. Moreover, the success of the measures based on the theory that the disease was essentially a house one is readily accounted for by the bug theory of infection which has now received such strong experimental support.

THE DESTRUCTION OF BED BUGS AS A PROPHYLACTIC MEASURE.

Just a year ago, several months before Captain Patton's successful feeding experiments, I arranged with Mr. Price for him to try the effect of repeated attempts to destroy all forms of insect life in the infected houses and those immediately around them in a coolie line[2] in which cases of kala-azar continued to arise in each cold weather period, leaving a second slightly infected one as a control. The houses were fumigated with burning sulphur, the beds were thoroughly washed with strong carbolic lotion, the clothes were either boiled in the same solution or destroyed, while the blankets were all burnt as being most likely to harbour bugs, new clothes and blankets being supplied. In the line which was thus treated six cases had occurred during the cold season of 1905–06, all in adjoining houses, and the disease seemed to be slowly extending, so that Mr. Price considered this spot to be "a regular hot-bed of kala-azar."

I have just received the results of this experiment up to the beginning of February, thus including three-fifths of the cold season, when fresh cases of kala-azar mostly appear, and so far no coolie has been attacked in the disinfected lines. Satisfactory as this result is, it must be admitted that it is not quite conclusive, because in the control slightly infected coolie line, which was not disinfected, there have also been no fresh cases of the disease, although this is not altogether surprising, as since last year all the cases in this control line have either died or recovered, leaving no foci in it from which infection was likely to take place, so that, as Mr. Price remarks in his letter, new cases would have been much more likely to have occurred in the disinfected than in the untreated lines.

The result of this effort to destroy bed bugs in the houses infected with kala-azar is, at any rate, most encouraging, and in view of Captain Patton having now proved that the parasite can develop into the flagellate stage in the stomachs of bed bugs fed on kala-azar patients and kept at the right temperature it may safely be laid down that somewhat similar disinfecting operations to those just mentioned should be carried out in all houses from which kala-azar patients are received, for this measure may be expected to do much towards preventing the disease running through the families of poor Europeans in the way I have described, and the terrible mortality in children in particular may be greatly lessened. By these means it is not too much to hope that as much may be done to reduce the present terrible loss of life due to the sporadic form of kala-azar in Bengal and Madras, at any rate among Europeans, as has already been accomplished in limiting the spread of the epidemic in Assam and stamping it out in coolie lines; and thus the knowledge regarding the life history of the parasite obtained by the investigations of the last four years may supplement and extend the scope of the prophylactic measures previously put into successful operation to stem the progress of the Assam epidemic of kala-azar.

I have now completed my task, and although I have necessarily had to dwell a good deal on my own work, especially when treating of the epidemiological and clinical side of the subject, on account of the very exceptional opportunities which I have enjoyed of studying those aspects of the question, I have also endeavoured to do full justice to the invaluable work of the numerous observers who have added so much to our knowledge; and in concluding I wish to emphasise the fact that the great advances made during the last few years in our knowledge of the most terrible of all tropical diseases afford a pleasing instance of the recent increased interest in tropical affections leading to combined work in different places by a number of medical men, all happily of British nationality.

[2] By a coolie line is meant a collection of rows of houses in which the garden coolies reside.

ABSTRACT OF

The Morison Lectures

ON

INSANITY, WITH SPECIAL REFERENCE TO PROGNOSIS.

Delivered before the Royal College of Physicians of Edinburgh on Jan. 28th and 30th and Feb. 1st, 1907,

BY A. R. URQUHART, M.D. ABERD., F.R.C.P. EDIN.,

PHYSICIAN-SUPERINTENDENT, JAMES MURRAY'S ROYAL ASYLUM, PERTH.

LECTURE II.[1]

Delivered on Jan. 30th.

I SUBMIT to-day a sheaf of tables and charts, which contain the various observations to which I desire to direct attention, and it will be observed that all cases of gross pathological nature have been deducted and that the remaining cases of obscure pathology only are tabulated.

First of all, cases in which alcoholism had a part in the etiology of insanity are set aside, whether these were cases in which the toxic effects of alcohol were symptomatic of the underlying malady or truly causative. The prognosis of alcoholism is indefinite and generally unfavourable. These persons are deeply affected by hereditary predisposition to abnormal conditions. Of 110 alcoholic certified and voluntary cases investigated, nearly 43 per cent. were hereditarily predisposed to insanity, and nearly 23 per cent. to alcoholism. The total neuropathic heredity was 70 per cent. I am not discussing drunkenness apart from insanity, regarding which my opinions have been repeatedly and energetically expressed—that it is a vice to be reformed rather than a disease to be cured. The insane drunkards are a class apart.

General paralysis is a disease which is practically incurable and comparatively rapid in its course. Out of 40 cases 23 were undoubtedly syphilitic and 14 were alcoholic. There is in our records presumptive evidence of syphilis in seven other cases. My experience leads me to believe that the hereditary factor is of importance in general paralysis. It used to be regarded as not a hereditary disease, an opinion which must be revised if my experience is general, for in reference to these 40 cases of general paralysis the heredity of insanity finds expression ten times, eccentricity four times, neuroses 12 times, and alcoholism 14 times. Rheumatism, gout, and tuberculosis are also noted. There was a distinct neuropathic heredity in 32 cases.

Turning to the cases of epilepsy reported, it will be seen that they are few in number, and I must add that all do not represent the ordinary cases of epilepsy which crowd the wards of the great English county asylums. The cases of ordinary uncomplicated epilepsy only amount to five. 11

[1] Lecture I. was published in THE LANCET of March 2nd, 1907, p. 572. The lectures were illustrated by statistical tables, charts, and clinical observations.

WELLCOME INSTITUTE LIBRARY